

A)

	Motif 1	Motif 2	Motif 3	Motif 4
Rv2837c_Mt	VGWVCHVEDPDTIGAGLALALVDGCG [35]	VDLVVTVDPSPVDRLGALG [6]	RELVVVDHHSND [10]	SADSTTTWAAILDANGKPIDPRVACIYAGLADTGSFRWASV
s111253_Ssp	DLILCHQTPDFPVLGRAVGLAKLHGSR [34]	IRSLIVDQGGDRLGKAA [8]	RQVAIVDHLNSP [11]	AVGASTTLLIVEKLQRADISLSNWVEASWMAIGIHVDTGSLTFTQT
NGPA_Ng	IVIFHHVRDPGCLGAQCGFLHLKANF [32]	EALAIWDPANYKRIELRE [7]	KAVERTDHPHED [11]	SYVACCCQIVEMATVAKWTIPPVAAATLLYTGIVDSSNRFVSN
YTQI_Bs	IILHRHVRDPAYSQCGTEILRETY [30]	GALVIVDPANQQRIDRQ [4]	AKLWCDHPHED [13]	SUSSEMIYELYLEGGHGHKLNKTAELIYAGIVGTGRFLPNT
AF2029_Af	LGIFTHDHPDSSNSAYALREIAKQFD [37]	YDAFAIVDSSGPGVNSIP [3]	DISIVDHPHAK [10]	DVGATATLTIVYIKELKITPSKITALATLALFFGKSETDEFEKNTR
MJ0977_Mj	NKILLVTHDDELTSALQKLAERLN [23]	YDLITFADLGSGQKMIKE [11]	DKIIEVDPHQP [18]	GAETCGAGSVSLFAKAIINNDWIDLAKYAVILGAVGDIQNIIEGKLI
MJ1198_Mj	RPIIRHHDNDYCGGIALEKALPII [46]	LPLVILNDGSTDEDIPI [7]	IEVIVDHPHESG [85]	KGRTYDREYLEKIALCMDFEAFYLRFWDKRGIVDILATNIKEF
HP1042_Hp	MQVYHSHDILGYACQLVSKQFFKNIQ [27]	EFLLIVSDNLNLNEAYVL [13]	IQQLVDHHSK [19]	IVVEFLKHYALEPKNTTWLEPLVENVNSVDINDTQGVGFELG
RecJ_Hi	QXIVIVGDPDAGATSTALSVALRQLG [31]	VQLAMTVNGVSSFDGVAF [5]	IRVAVDHLHPE [33]	LAURAKFRELGIFTAETQNFDTDLDLVALGTIADWVPLDQNNR
RecJ_Hp	TEILVVGVDADGVISSAIWAKFFESLN [27]	APLIIVDNGINAFEARF [5]	YTLIIVDHLCLH [27]	LVAFLVCYGIHQILGKESKSHSSSELLCAGVATIDMMPLTFFNR
RecJ_Ssp	EKVITNGDPDAGITSTAVLWEGLGQFF [32]	TCLIIVDTPGTSWLDIIVY [5]	MDVIVDHPHTLP [27]	VAFKLVERALVNYQPTVPQOPLDLDLVAIGLIADLVTLQGDOR
YYBQ_Bs	ILIFGHQNDPDTICSAIAYADLKNKLG [36]	VNGVILVDHNERQOSIKDI [3]	QVLEVIDHHRAN [12]	FVGCTATILNKNYKNNVKEIEIAGMLMSAIISSLSLFKSPYC
ICRA_Sg	ILVFGHQNDSDAIGSSYAFAYLAREAY [38]	AEQVILVDHNEFQOSVADI [3]	EVGVVDHHRVAN [12]	PVGSASSIVYRNFRKHSVAVSKEIAGMLSGLISSDTLLKSPYT
Y608_Mj	RYVVGHKNDPDTIASAIVLAFYLDYCP [31]	GKEIIVDHPSEKSSQSFDDL [3]	KLIAIVDHPHKVGL [19]	IAELYFKDAIDLIGGKKELKPLAGLILLGSAIISDTVLFKSPYT
AF0756_Af	VYVVGHKNDPDSVCSAIFAYLWKNK [46]	GKKVANDHPSEKATVDGI [3]	EVVAIVDHPHKIGD [12]	PVGCTATVILKLLFDKTVGEIPKDIAGILLSSILSSDTVLFKSATT
U60409_Lm	TWVQNEGNDPSIVGCIYLANLFDKQ [44]	QTAHNVDLTAALNASVLY [14]	RVVGVVDHPHEDQ [11]	LRTVGSACTVITELVRECEDEVVCPPTLTITAPIVDTVNFEPAPQK
PX1_Sc	TICVGNESNDPSIASAITSYCYIYN [62]	ELNSIVDNDTTPKLNKY [2]	NVVGIVDHPHFDLQ [14]	SCSSLVFNWYWEKLGQDREVWNNAIPLNGAILLDTSNWRRKVE
PRUNE_Dm	HLVWGNESDPSAIVSAVTLAFVYQRH [48]	DVNVIVDHPVSLAPNVT [1]	NVTEIVDHPHLED [18]	SVGSCATVIAQRYLAEDQPRSTVAQLLHATIVDTINFAFAAK
h-prune.1_Hs	HVVVLGNEADPDTSTVSALALAFYLAKTT [52]	QLTLLVNDHPHILSKSDIAL [2]	AAVAEVDHPPIEP [12]	LVGSCATVITERILQGAPEILDRTRALLHGTIILDCVNMDLAKIG

specific motifs

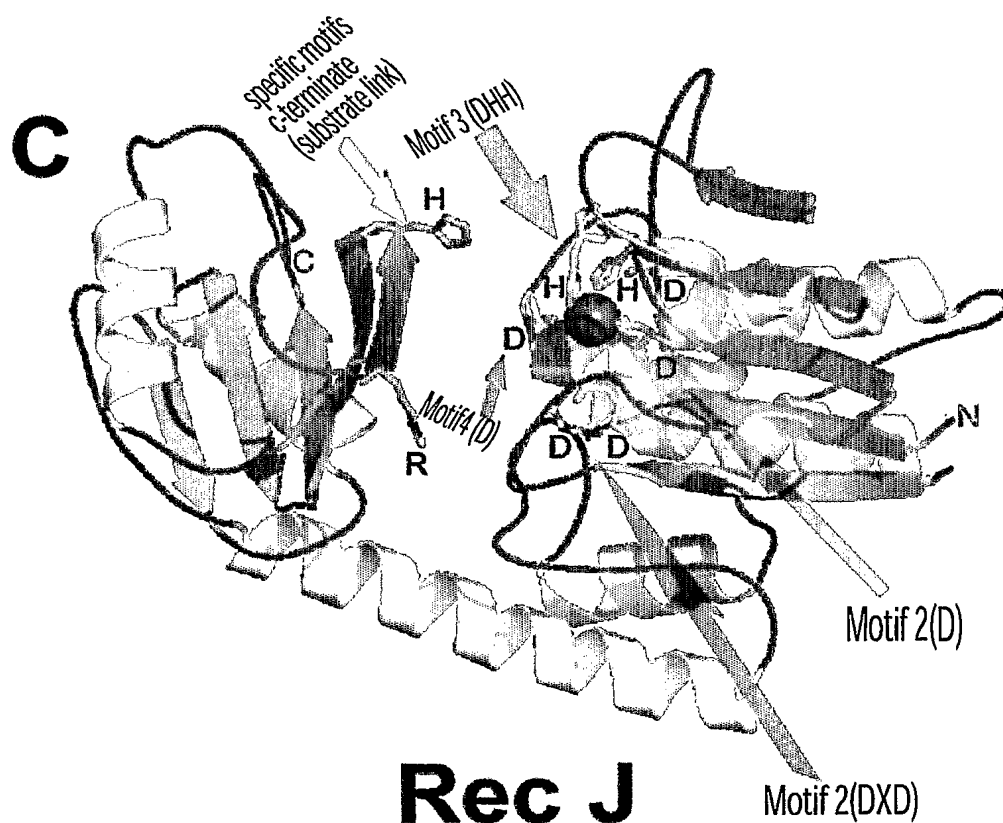
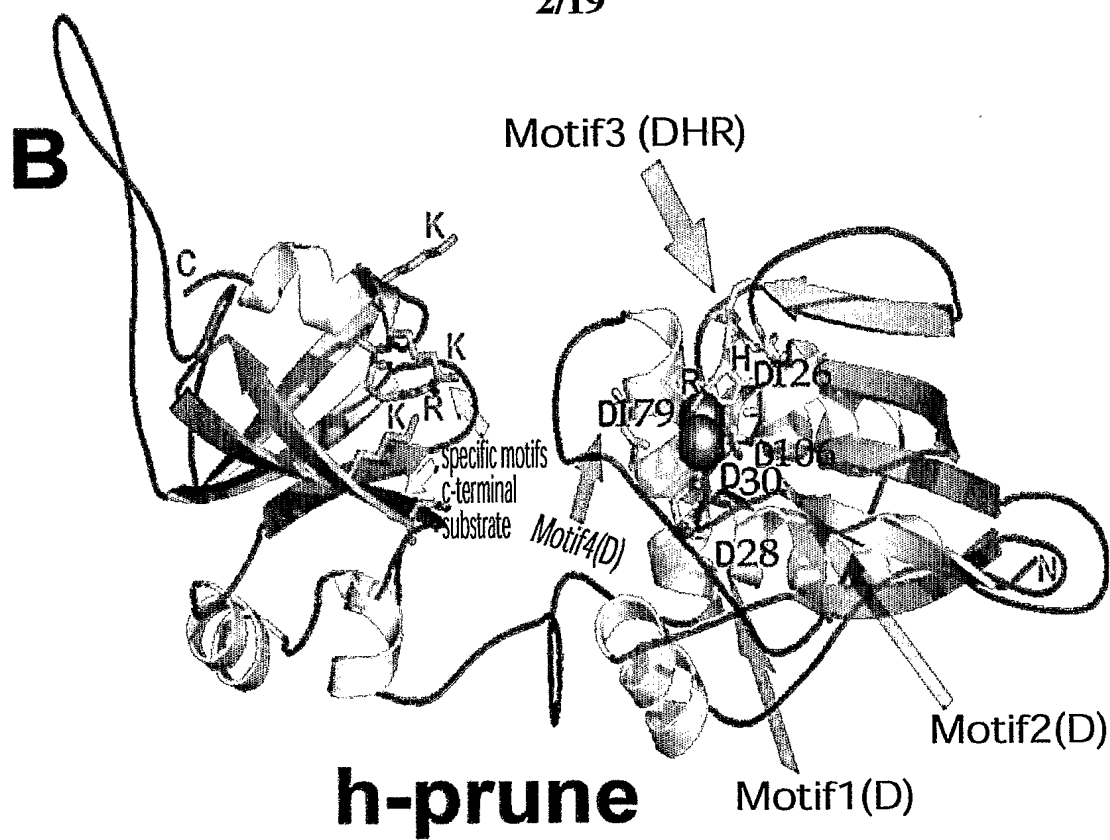
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s111253_Ssp	[123] DTDLTQLLEPYGCGGHAQAANLRDV	1653244
NGPA_Ng	[102] GINVRDIAIKYGGGCHNNSAGAITNK	1045875
YTQI_Bs	[103] GPVINGLARKYNGGHPPLASGASIYSW	2293259
AF2029_Af	[102] EVLRAFQDVGAGGHAHAGAQIPLG	2648507
MJ0977_Mj	[254] AIKYASEKVGSGGCHKFACGAYIPDN	2128614
MJ1198_Mj	[109] QLMBEIPEASLDGCGHECAGSLKFEVG	2128720
HP1042_Hp	[137] CDVCELSQVCFNGGCHRNASGGKIDGF	2314198
RecJ_Hi	[168] RIHSQHPNWLKFGGHAMAAGLSIREE	1172895
RecJ_Hp	[155] DALNGVSSILLGYGGRQACGLSVEKN	2313437
RecJ_Ssp	[165] ALLHSQRHMLGFGGHPFAAGLSPLD	1652638
YYBQ_Bs	[31] DLSKKTVEBELISLDANEFTLG [75]	TALLKGVVSRKKQVVFVETD 586817
ICRA_Sg	[31] NLAKSABELIDIDAKTFELN [75]	HAFLAGAVSRKKQVVPQLTE 1743856
MJ0608_Mj	[32] VVGKLPKEIINMDFNFDEN [74]	SVFLEGVMSRKKQVVPPLER 1591318
AF0756_Af	[32] AVDDLTAMDITIKRDYKDFDMS [75]	SVWLDGVMSRKKQVVPPLER 11498362
L2759.9_Lm	[36] DVALSVPQILRRDYKQFSEK [105]	YSISDPSISRKK-LVPALSE 1407725
PX1_Sc	[41] DIKGFVSVDILKKDYKQFNQ [97]	MFQQLNVEATRKQVVPYLEE 730369
PRUNE_Dm	[37] DISKLTLEVERDKMKVLQTD [97]	LROHNVQATRKH-ILPVIYKR 1079081
h-prune.1_Hs	[34] DVSGLTTEQMERDKQXTIYRQ [94]	YLQNTQVSRKK-LIPLLOE 11245938

Family 1

Family 2

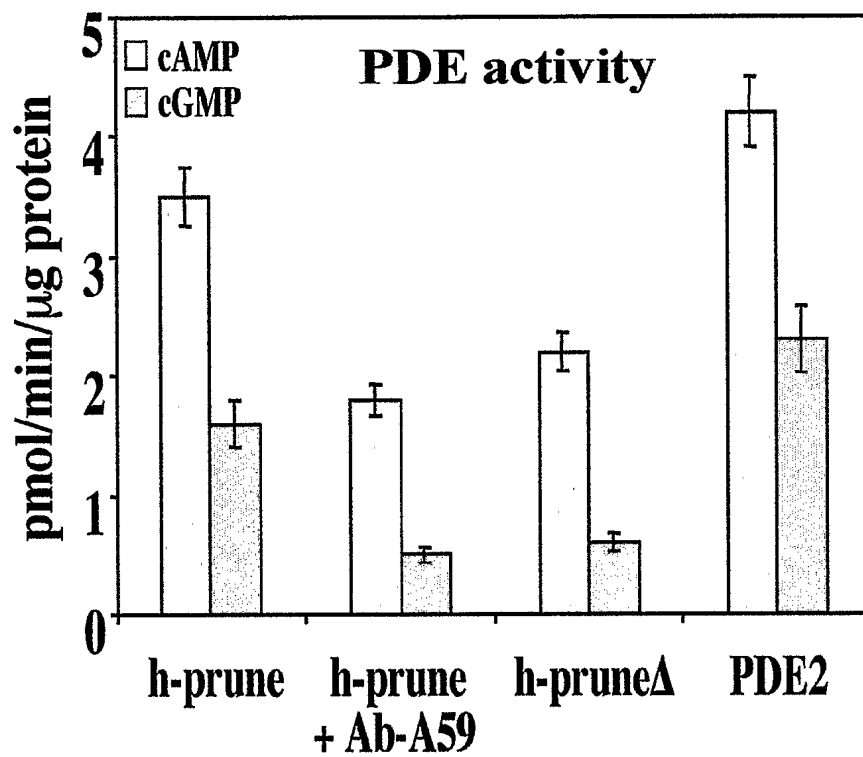
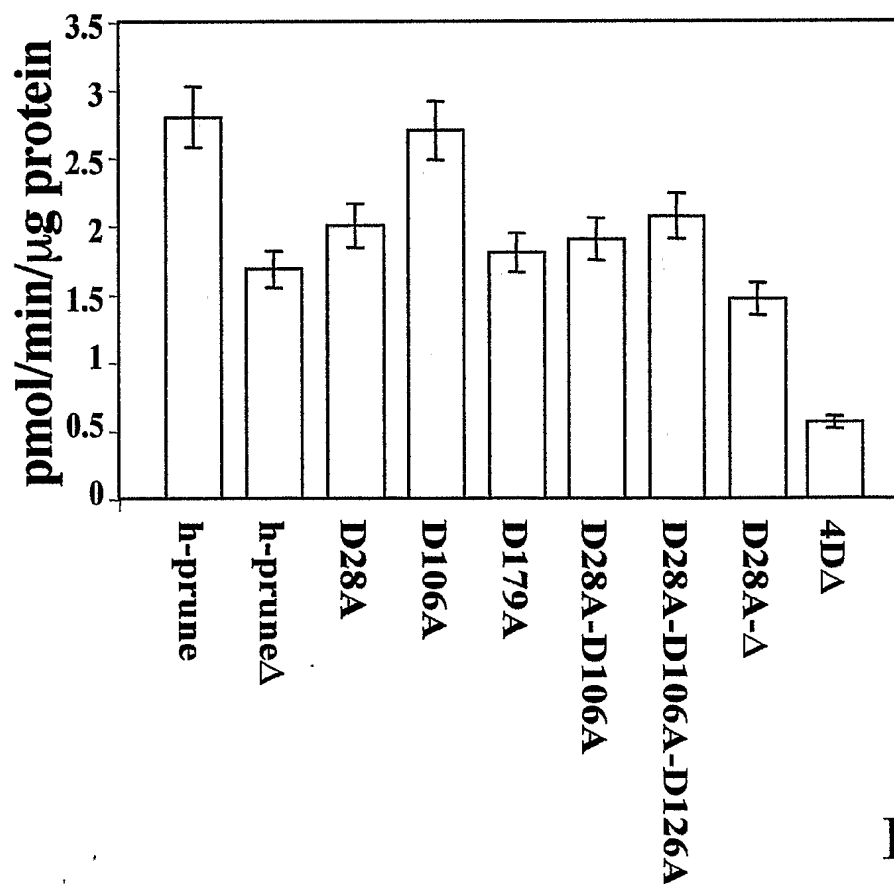
Fig. 1

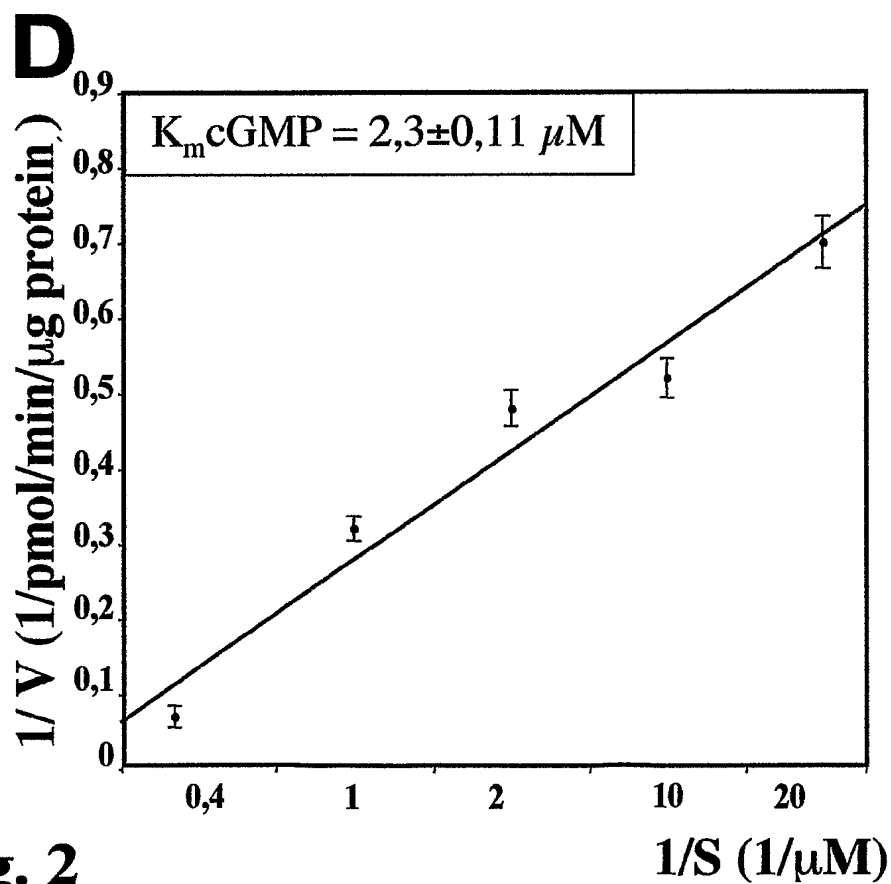
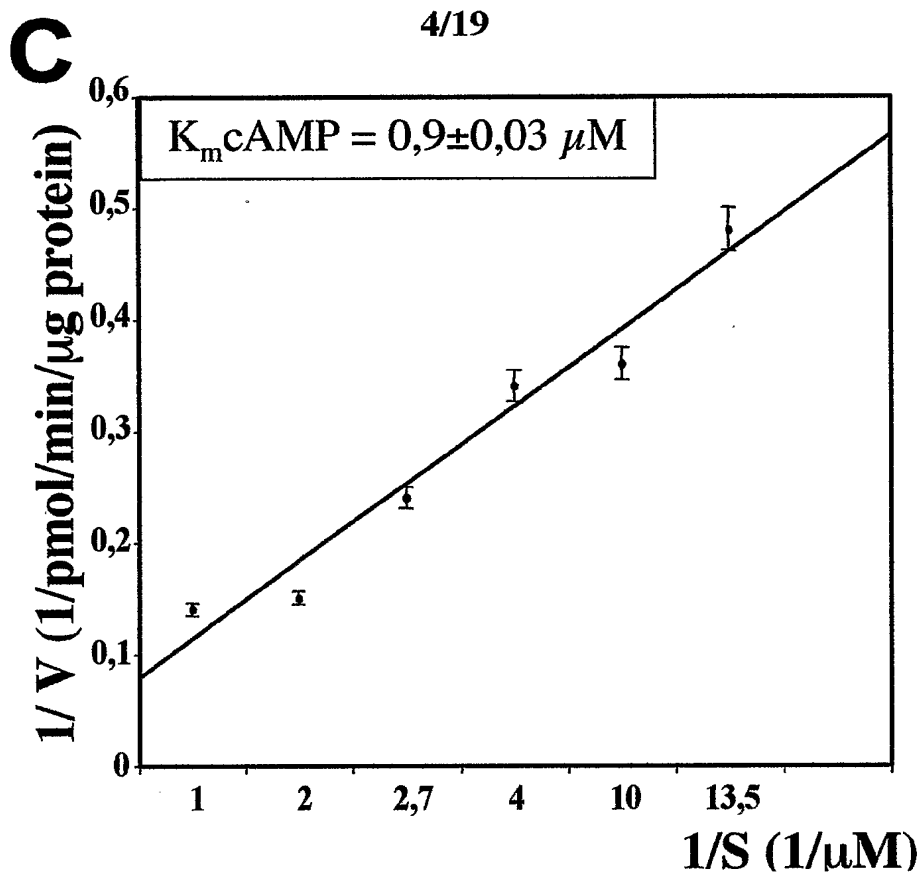
2/19

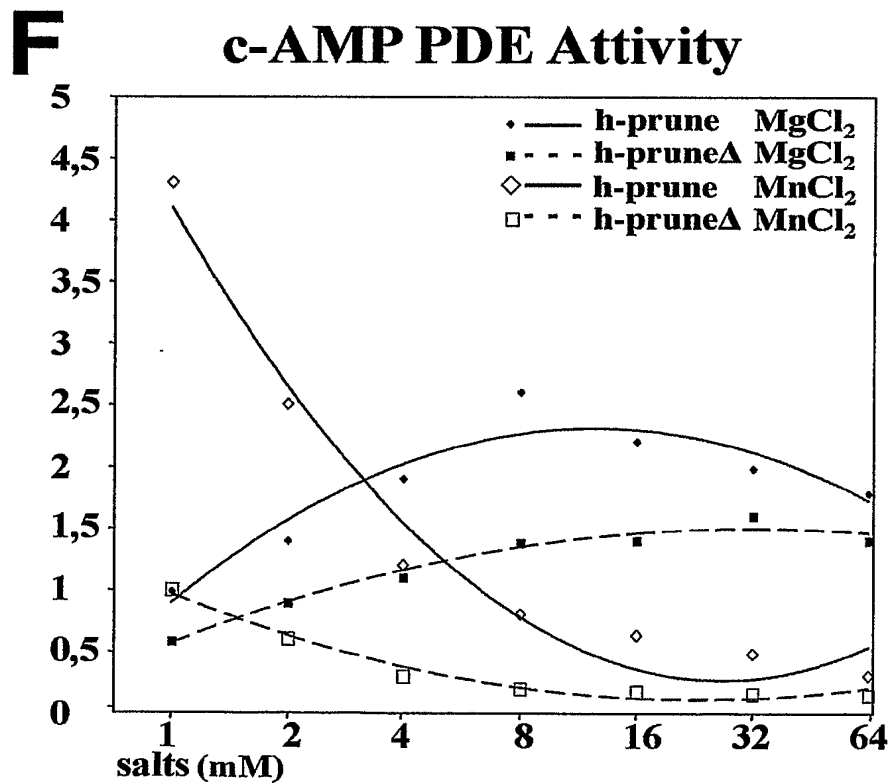
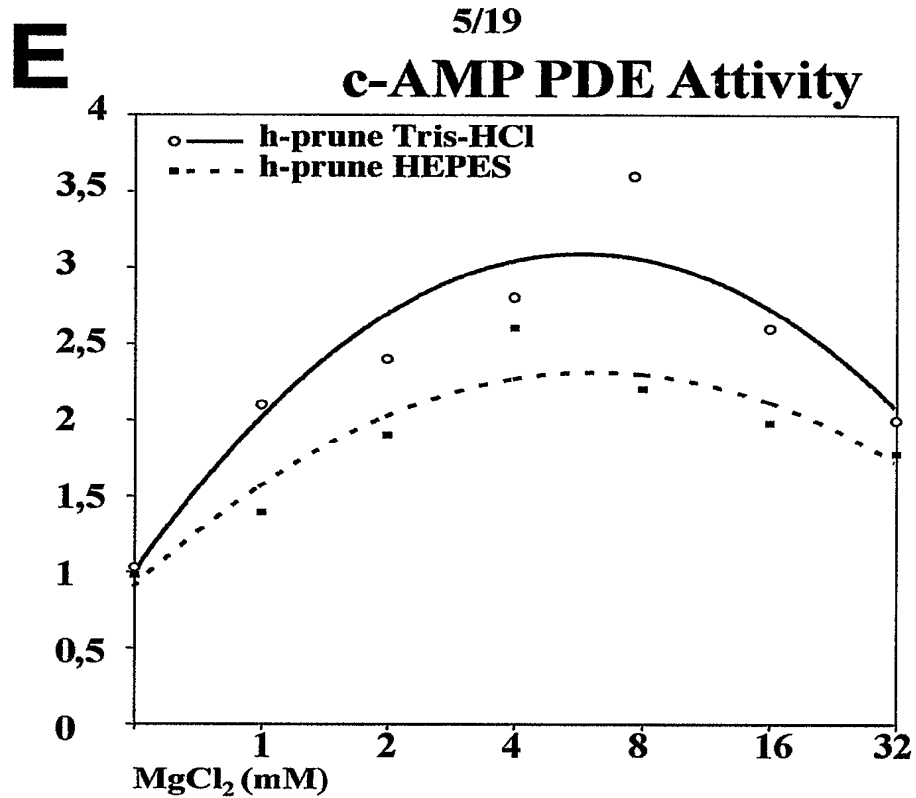
**Fig. 1**

A

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**B****Fig. 2**

**Fig. 2**

**Fig. 2**

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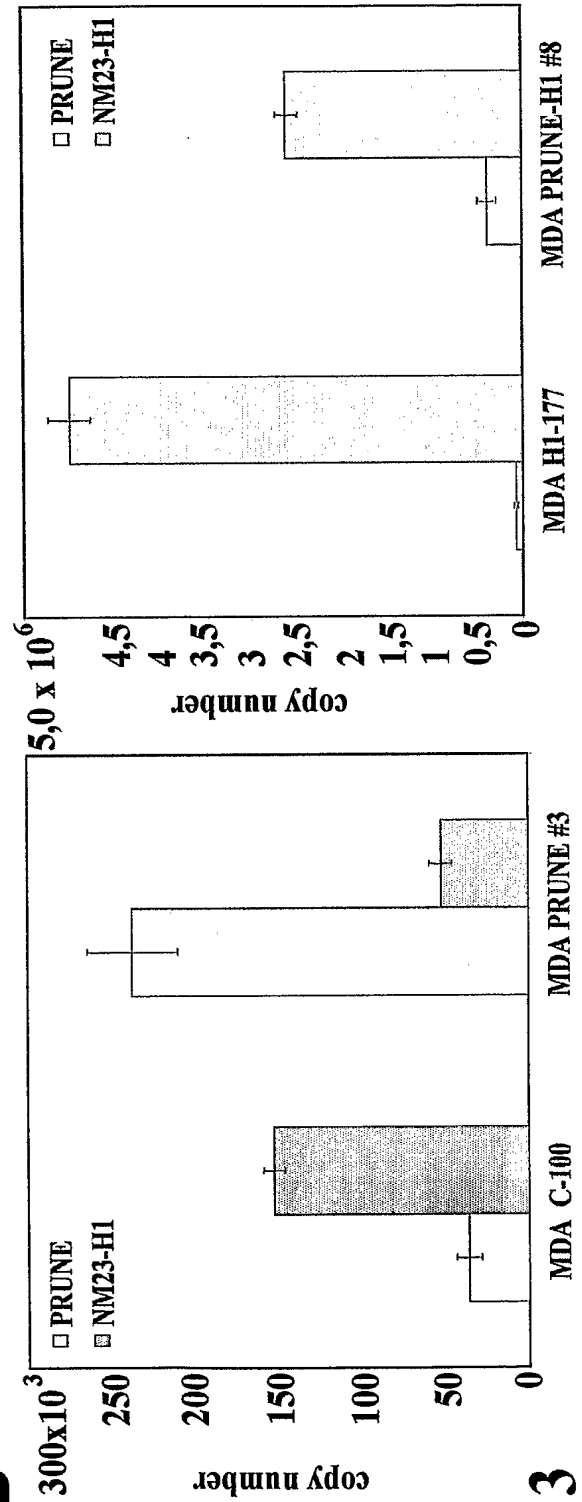
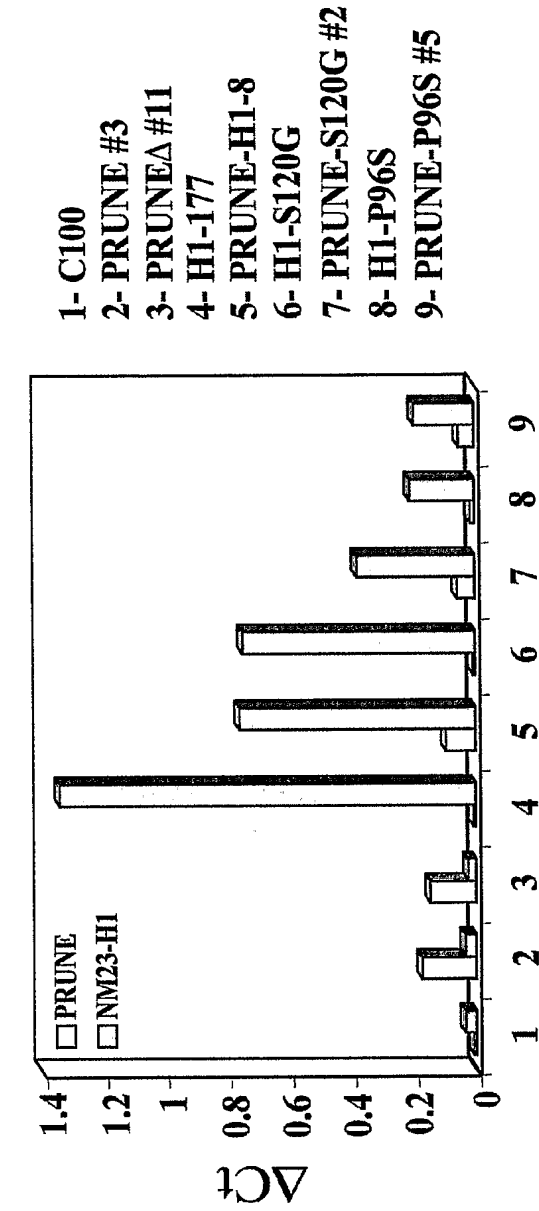


Fig. 3

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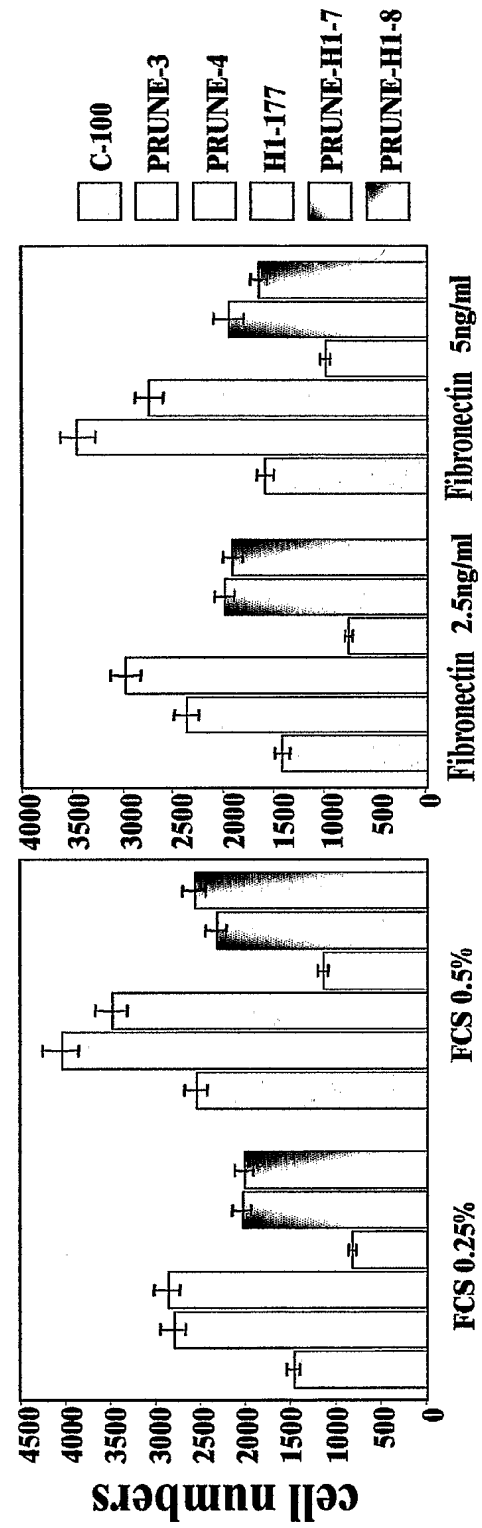
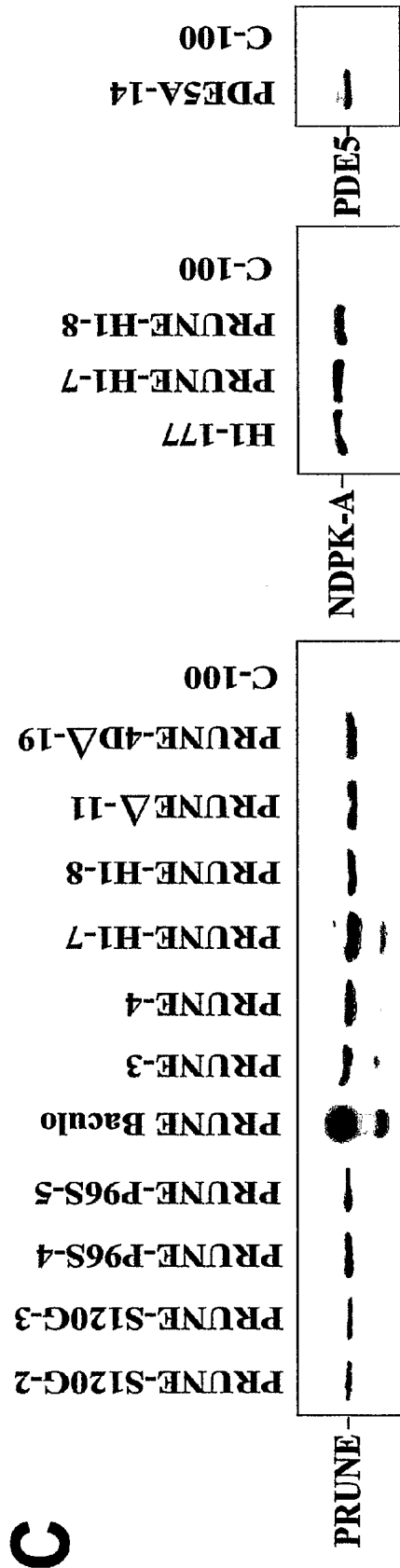
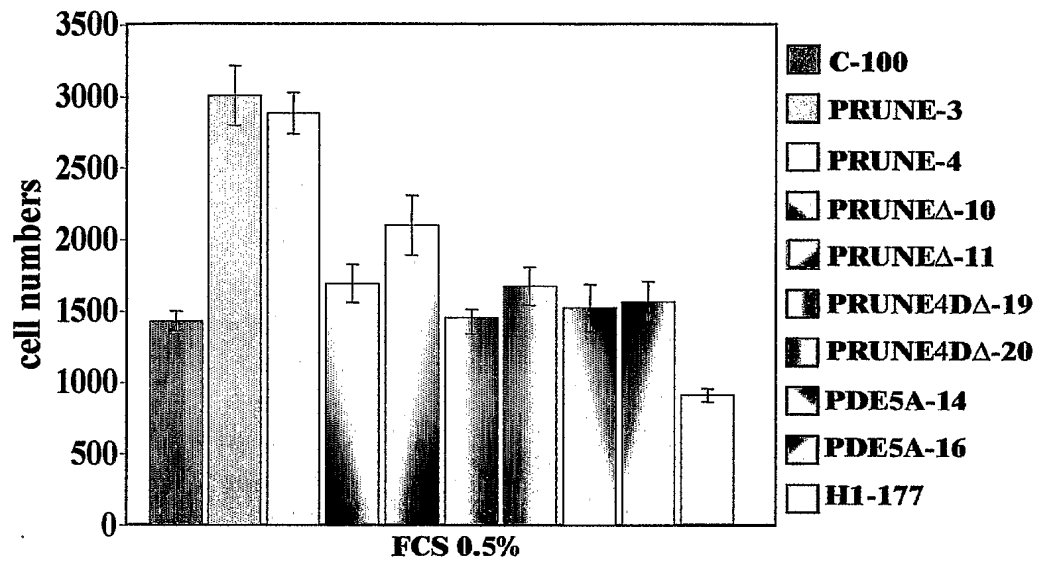
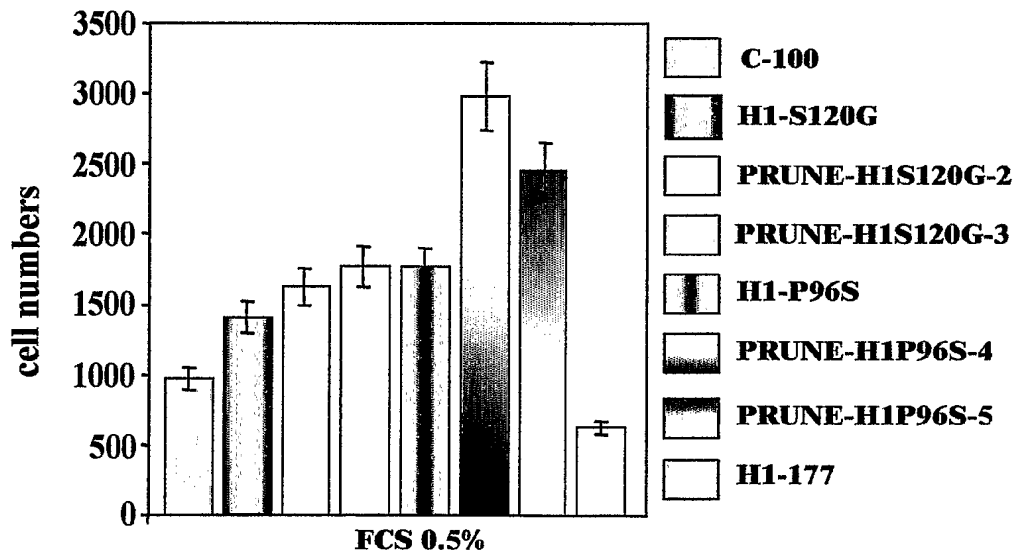
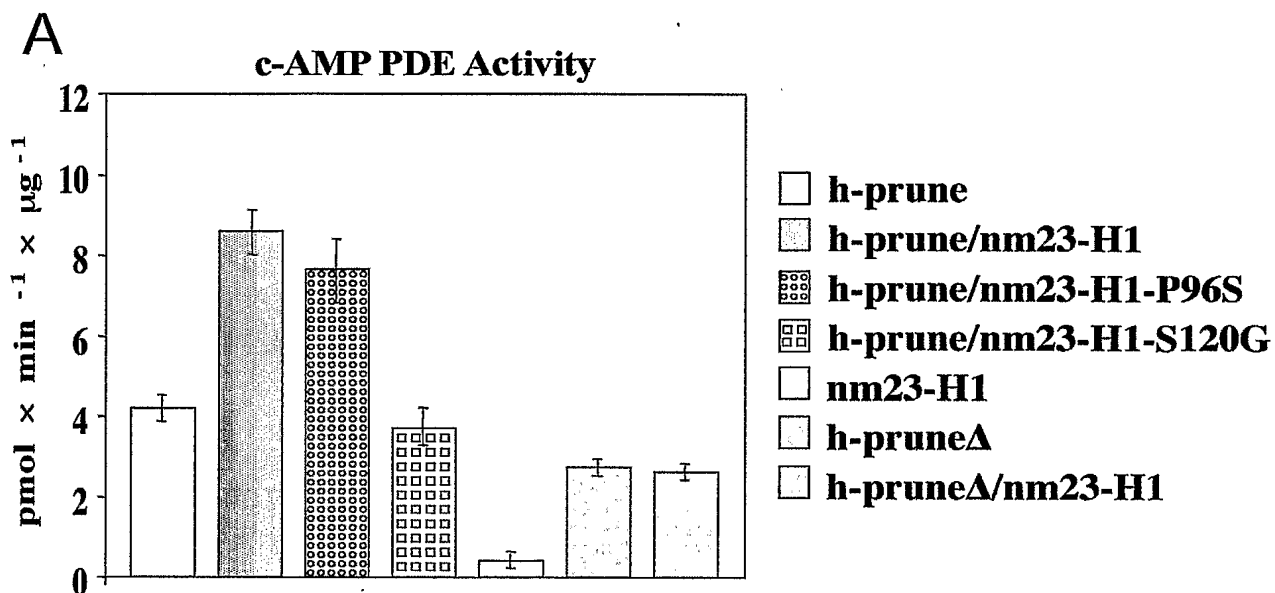


Fig. 3

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E**F****Fig. 3**

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**B**

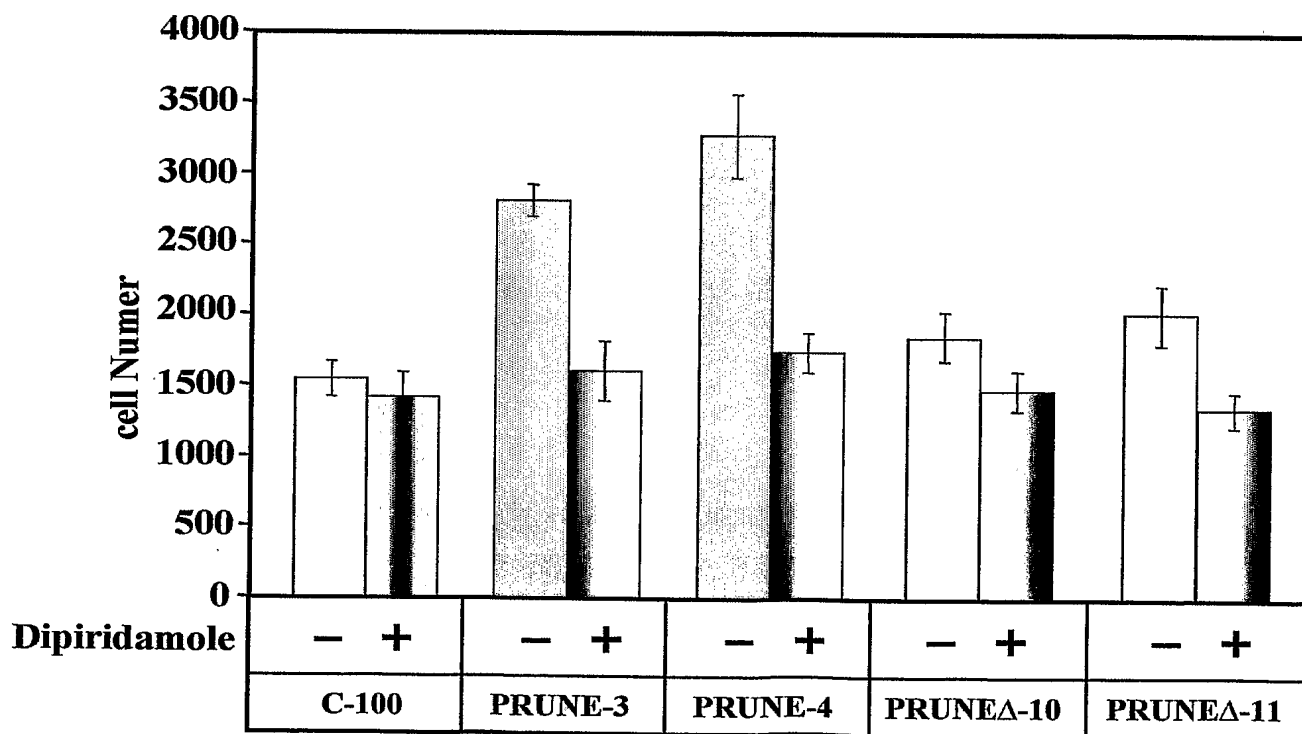
lone name	PDE h-prune Activity (pmol \times min ⁻¹ \times μ g ⁻¹)	Motility cell number
MDA C-100	3.8 \pm 0.7	1548 \pm 84
MDA H1-177	2.2 \pm 0.4	928 \pm 73
MDA PRUNE #3	35 \pm 5.3	2812 \pm 294
MDA PRUNE #4	28.7 \pm 2.5	3272 \pm 271
MDA PRUNE Δ #10	16.8 \pm 1.2	1682 \pm 64
MDA PRUNE Δ #11	14.6 \pm 0.9	2087 \pm 97
MDA PRUNE-H1 #7	18.8 \pm 2.6	2048 \pm 93
MDA PRUNE-H1 #8	22 \pm 4.2	2006 \pm 87
MDA H1S120G	2.4 \pm 0.8	1328 \pm 54
MDA PRUNE-H1S120G #2	4.4 \pm 1.6	1624 \pm 89
MDA PRUNE-H1S120G #3	5.3 \pm 1.4	1767 \pm 108
MDA H1P96S	3.0 \pm 0.3	1742 \pm 38
MDA PRUNE-H1P96S #4	19.2 \pm 0.3	2982 \pm 184
MDA PRUNE-H1P96S #5	11.6 \pm 0.4	2448 \pm 143

Fig. 4

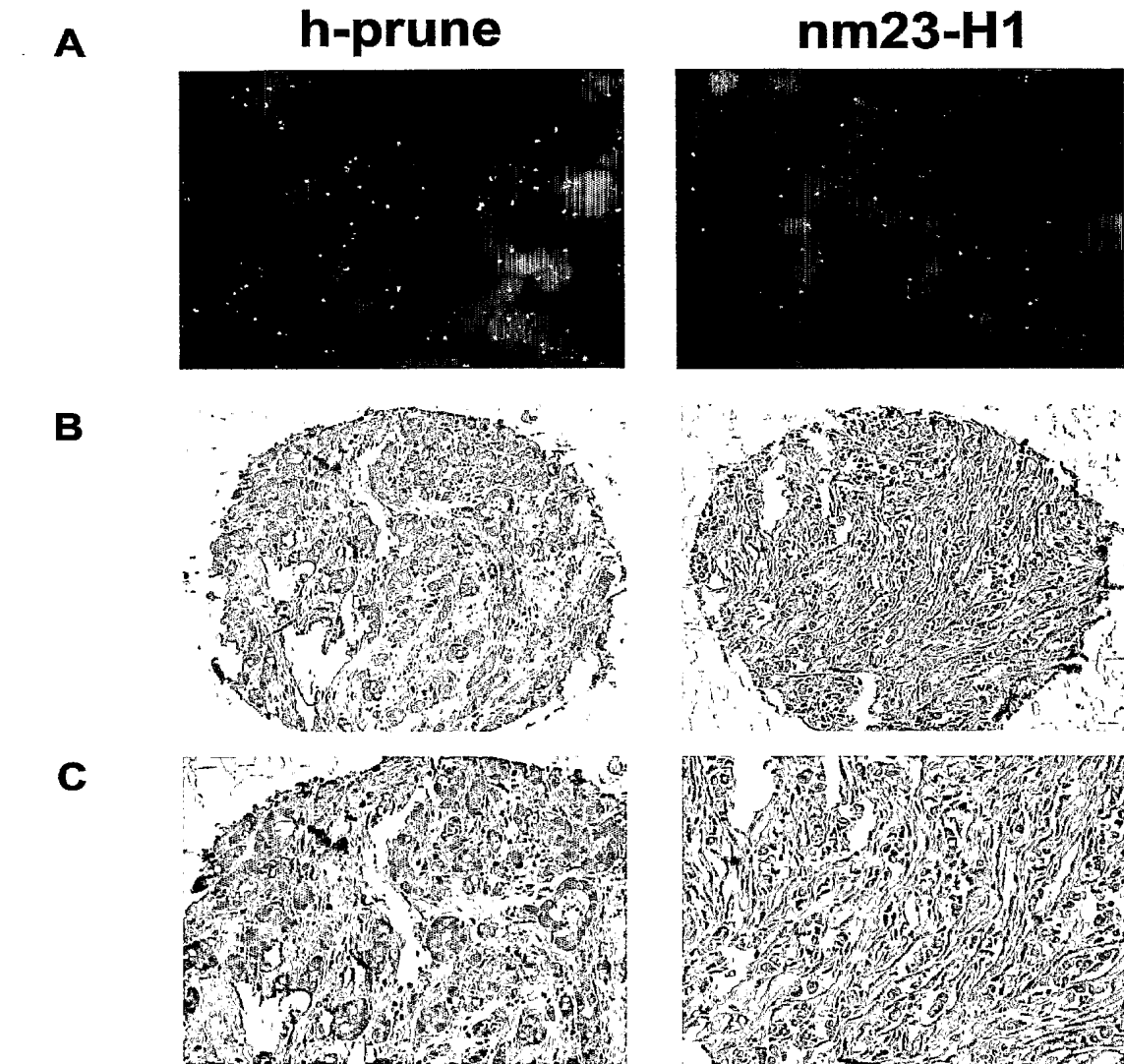
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A

Inibitor	Selective for a PDE type	IC ₅₀ μM	h-prune IC ₅₀ μM
Cilostamide	PDE3	0.05	>100
Dipyridamole	PDE5/6/9/10/11	0.9/0.38/4.5/1.1/0.37	0.78±0.05
IBMX	non selettivo	2-59	40.2±0.8
Milrinone	PDE3	1.3	>100
Rolipram	PDE4	2.0	>100
Vinpocetine	PDE1C	8.1	22.3±1.1
Zaprinast	PDE1/5/6	6.9/0.76/0.15	>100
Sulindac	cGMP PDEs	—	>100

B**Fig. 5**

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**D**

Immunohistochemic (IHC)	IHC Grade	Fish Analysis			
		PAC h-prune (1q21.3)		PAC nm23-H1 (17q21)	
		Disomy	Trisomy or more	Disomy	Trisomy or more
h-prune	+++ / ++	7 (12%)	22 (37%)		
	+ / 0	30 (51%)			
nm23-h1	+++ / ++			1 (2%)	
	+ / 0			54 (98%)	
analyzed cases TNM_I		59		55	

Fig. 6

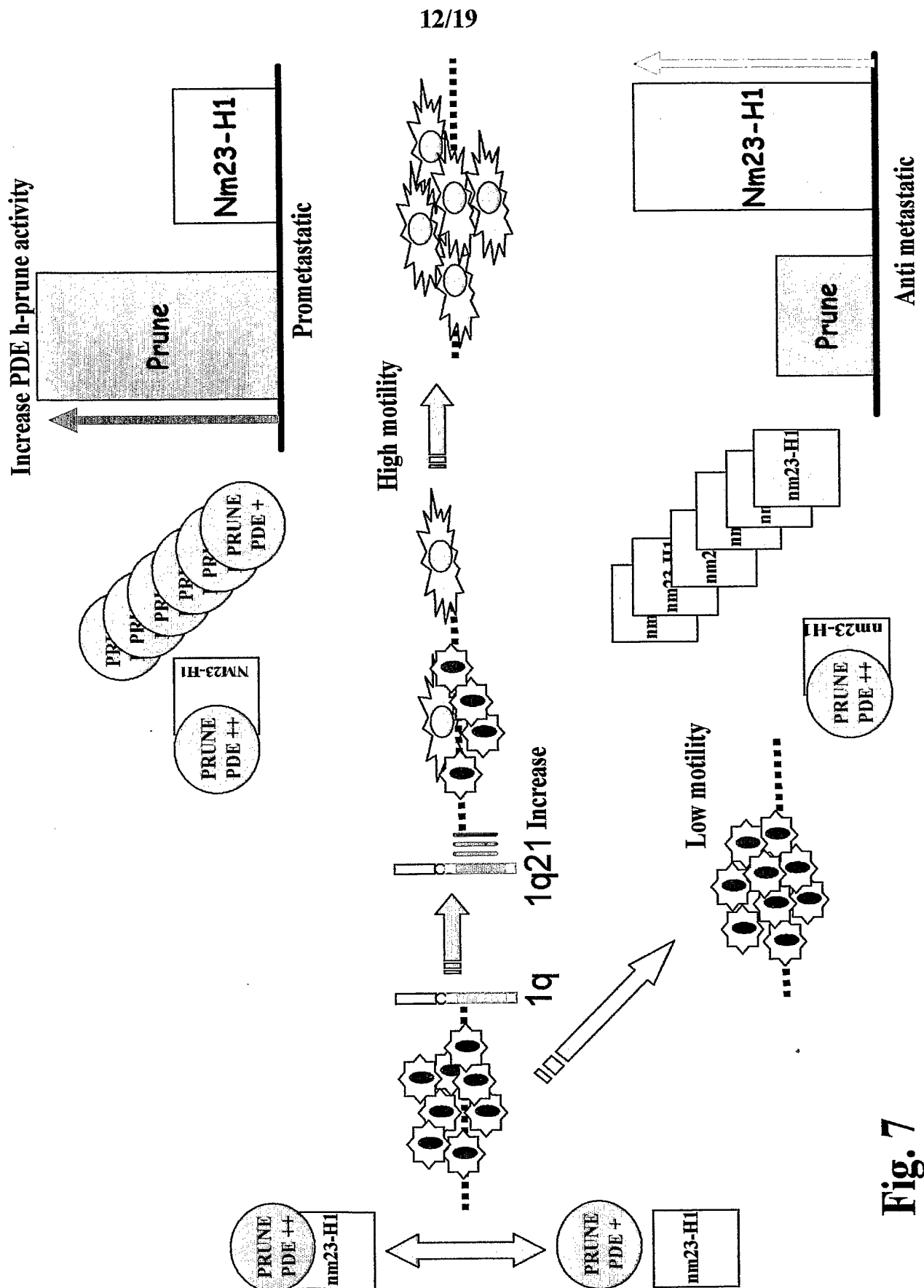
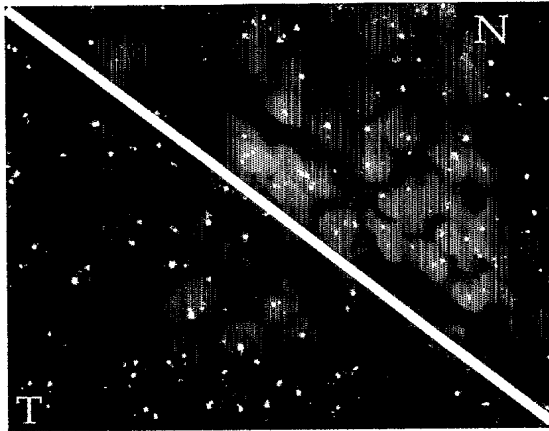


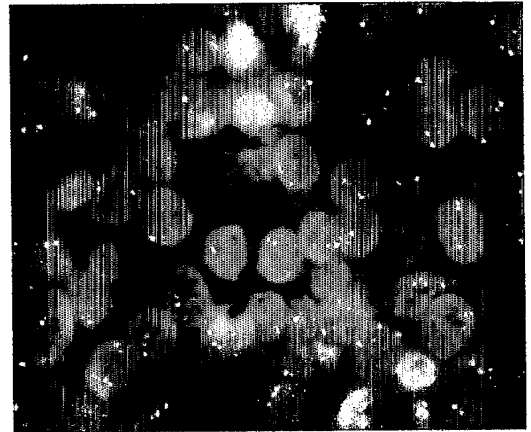
Fig. 7

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A

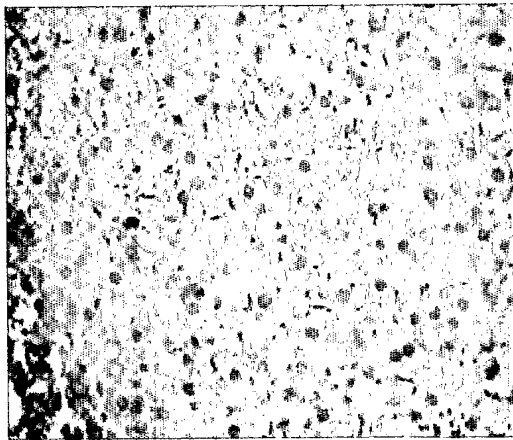


Normal and tumoral tissue

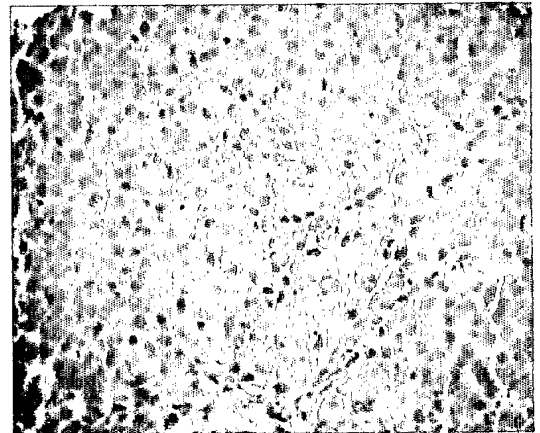


Tumoral tissue
(not metastatic)

B



Normal tissue



Tumoral tissue
(not metastatic)

Fig. 8

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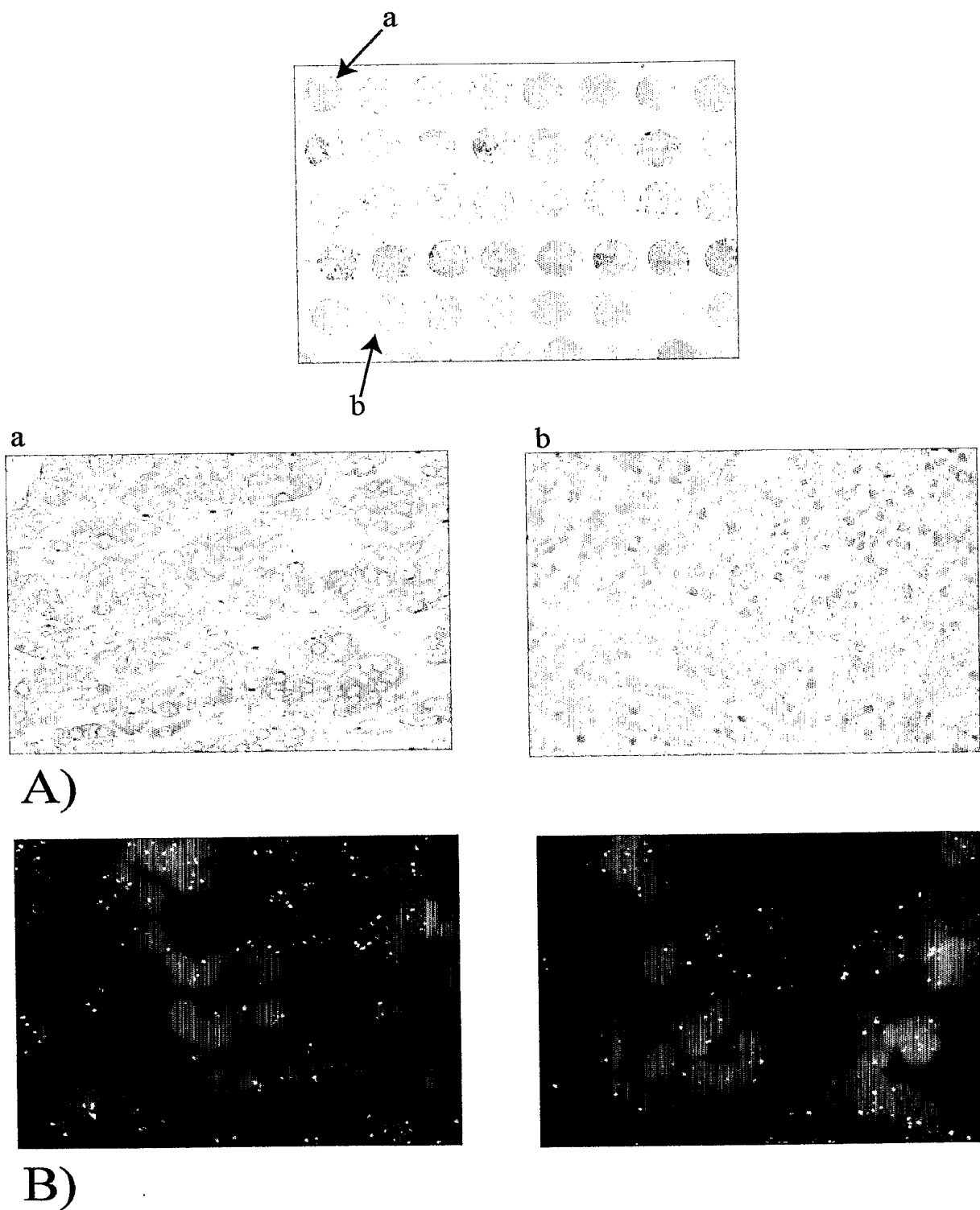
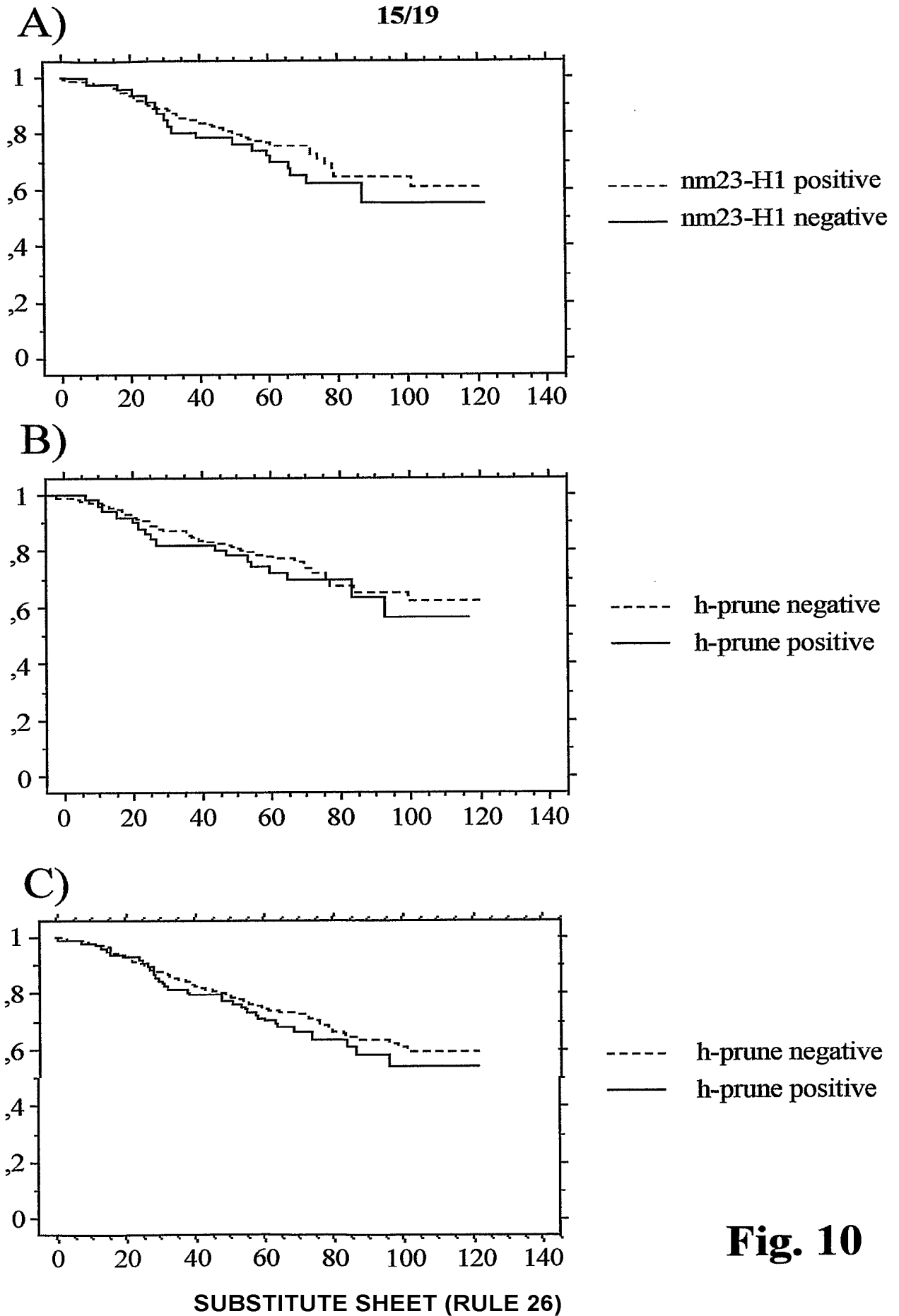
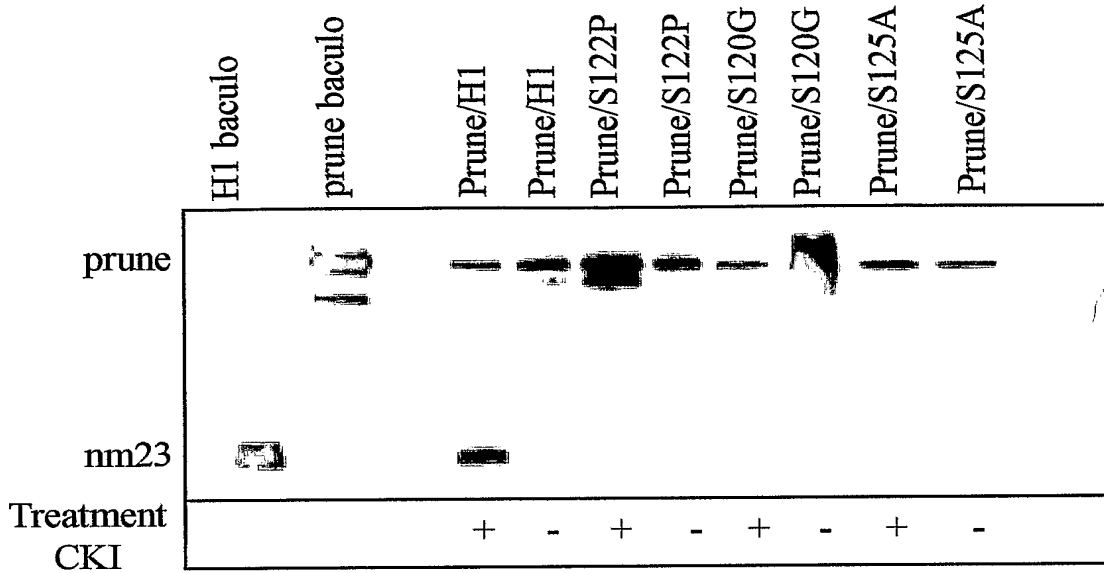


Fig. 9



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A)

MYDVPDYASLGSPVEMA
 NLERTFIAIKPDGVQRGLV
 GEIIKRFEQKGFRVLAMK
 FLRASEEHLKQHYIDLKD
 RPFPPGLVKYMNSGPVVA
 MVWEGLNVVKTGRVML
 GETNPADSKPGTIRGDFCI
 QVGRNIIHGSDSVKSAEK
 EISLWFKPEELVDYKSCA
 HDWVYE

B)

Fig. 11

Voyager Spec #1 MC[BP = 1344,6 2144,9]

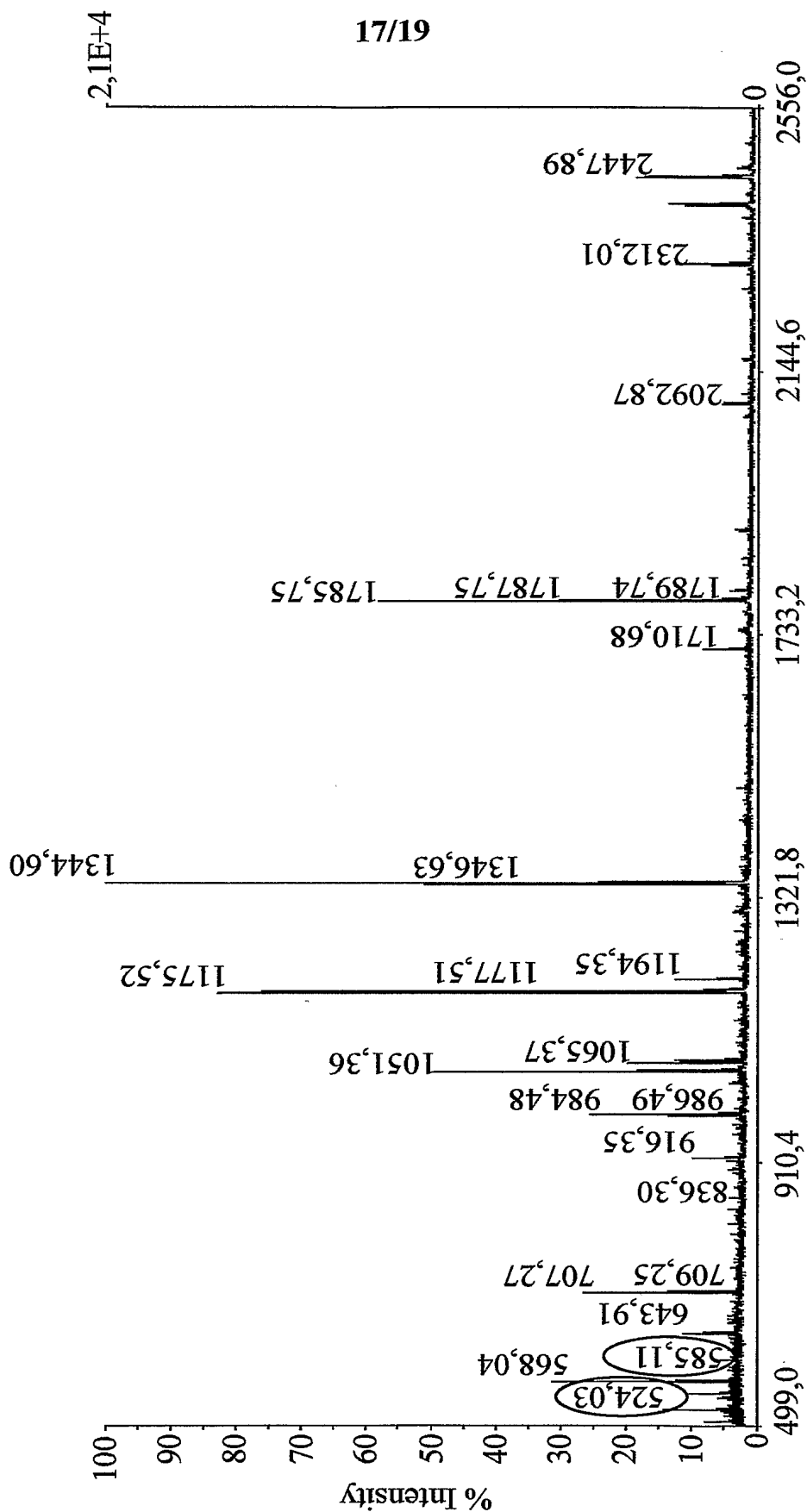


Fig. 11 C

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A

	1	2	3	4
CKIδ	+	+	-	-
Isoform Nm23	H1	H2	H1	H2

nm23 →

**B**

IC261	0h	2h	4h	6h	8h	0h
CIP	—	—	—	—	—	+
Phosphorecated nm23H1						
Total nm23H1						

C

	1	2	3	4	5
IC261 μMol		50	200	—	

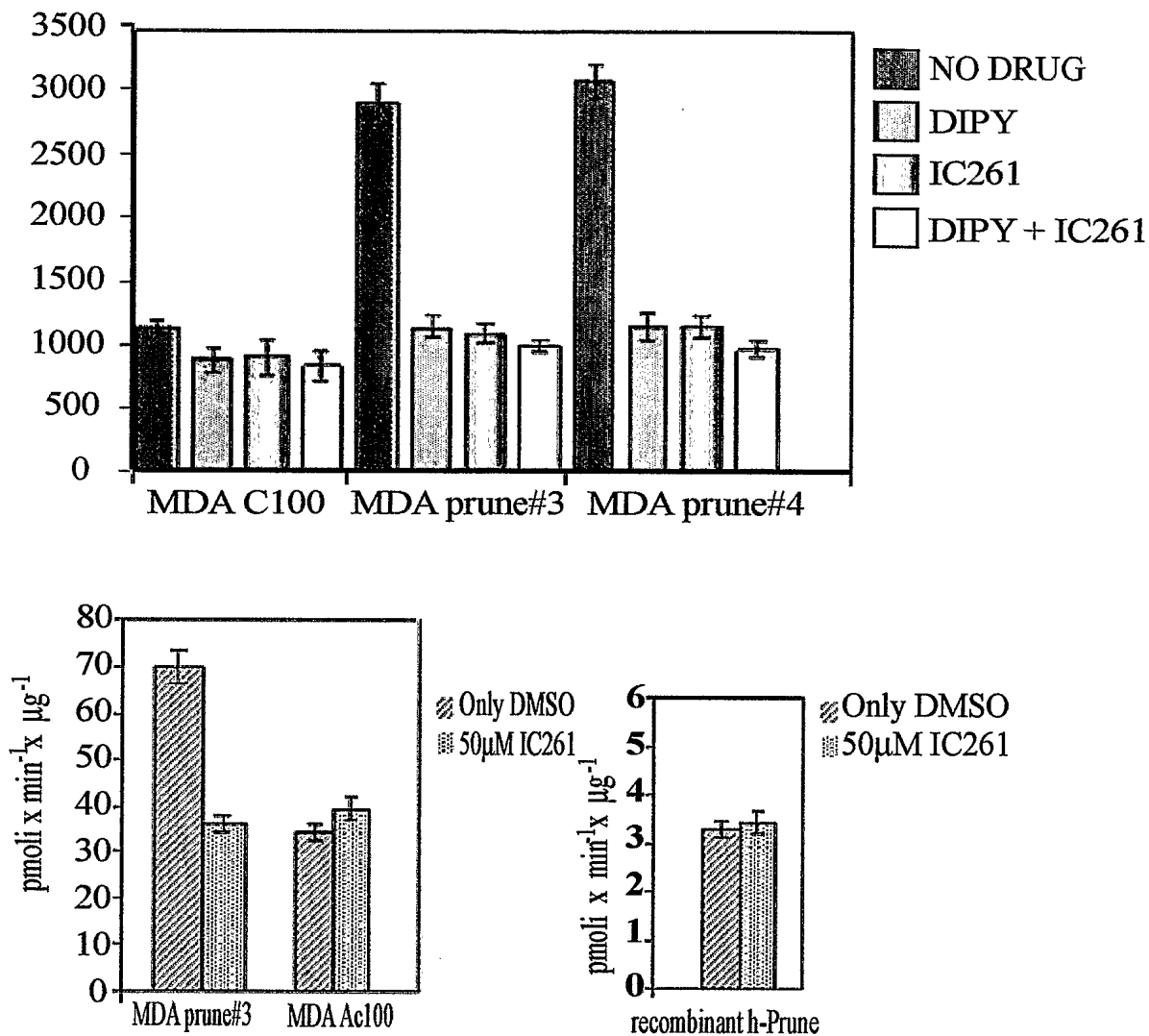
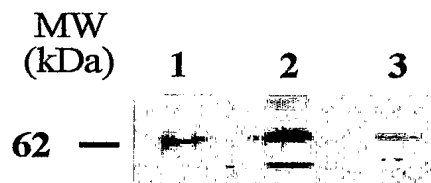
h-prune →



nm23H1 →

**Fig. 12**

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**Fig. 13****Fig. 14**